



Modern Trends in Complex Treatment of Patients with the Cervical Cancer

O.V. Bondar¹, A.I. Rybin², K.M. Doikova³

¹Professor, DSc, Department of Radiation Diagnostics, Therapy and Oncology, Faculty of Medicine, Odessa National Medical University, Ukraine;

²Professor, DSc, Department of Radiation Diagnostics, Therapy and Oncology, Faculty of Medicine, Odessa National Medical University, Ukraine;

³Dr, Department of Radiation Diagnostics, Therapy and Oncology, Faculty of Medicine, Odessa National Medical University, Ukraine.

ABSTRACT

Introduction: Complex treatment of patients with the cervical cancer has been studied less.

Aims: To assess the effectiveness of combined treatment (surgery + radiomodifier as chemotherapy and radiation therapy) in patients with cervical cancer.

Methodology: Retrospective analysis of case histories of 661 patients with cervical cancer. Patients received treatment from 2015 to 2020. All women were divided into 2 subgroups: in the main (n = 336) surgery, radiomodifier and radiation therapy and the control group (n = 325), no radiomodifier was used.

Results: An objective response after the first stage of treatment was achieved in 84.3% of patients in the main group and 59.4% of patients in the control group. Intra-systemic administration of cytostatics had a significant effect on the involution of infiltration in comparison with the effect of radiation only. In cases where neoplasm has not reduced, positive changes were observed: the exophytic part of the tumor, its bleeding and the volume of discharge decreased, superficial necrosis decreased or completely disappeared.

Out of 336 patients from the main group IB2-III stage, 87% of patients are in remission for more than 3 years.

Conclusion: The undeniable advantage combining radiation treatment with chemotherapy has been proven. Current standard may be considered as the weekly introduction of platinum preparations in the process of radiation treatment, as well as the use of fluoropyrimidine derivatives as radio-modifying agents. Nature and extent of early complications did not differ reliably in comparison groups.

Key Words: Cervical cancer, Gynecology, Chemoradiation therapy, Radiation therapy, X-ray, Radiomodifier.

INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide, and it has the fourth highest mortality rate among cancers in women.¹ According to the American National Cancer Institute, 13,800 women are diagnosed with cervical cancer in the United States each year, and approximately 4,290 patients die from this condition.² In Ukraine, the incidence of cervical cancer is 10.8% at age 18-29 years, and 12.5% at 30-54 years. In the mortality structure, cervical cancer was the main cause of death in 11.8% in the age group 18-29, and 14.2% in 30-54.^{3,4} FIGO staging is an effective tool for choosing a treatment for cervical cancer. With complex treatment with surgery and concomitant chemoradiation therapy (CCRT), cure rates up to 80-90% in the early stages (stages I-II) and 60% in stage III.⁵ In recent years, the Ukrainian

developed screening program for early diagnosis of CC with active identification of women suffering from background and precancerous processes has provided a remarkable reduction in the incidence level of cervical cancer. Yet due to a variety of social and economic reasons, the negligence rate is still high and climbing. In oncology, the situation is straightforward – the more advanced is the process, the fewer options are there with therapeutic benefit.⁶

The issue with cervical cancer treatment depending on the stage has already been mentioned as a pressing problem within multiple works.^{8,9,10} Since patients are younger compared to other localizations of gynecological cancer, the issue of organ-preserving treatment is of utmost importance. However, the need for a more radical option arises from higher autonomy and aggressiveness compared to hormone-dependent tumors.^{11,12}

Corresponding Author:

Katerina Doikova, Department of Radiation Diagnostics, Therapy and Oncology, Faculty of Medicine, Odessa National Medical University, Ukraine; Email: doikovaekaterin@gmail.com

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Three main treatment methods are surgical, combined, and combined radiotherapy, with radiotherapy being the primary treatment method and almost the only option at III stage. However, analyzing the history of the development of physical and technical support of radiotherapy, M. Weinberg (1994) observes that "...there is no increase in the effectiveness of radiotherapy in proportion to the improvement of its physical and technical base. Recently, it has been noted that the growth rate had decreased, significantly behind the expected levels with the use of new promising techniques, technical and technological means in radiotherapy (individualization, optimization, automation, computerization)." 13,14,15,16,17

Dissatisfaction with the results of treatment led to the development of various approaches and methods to complement radiotherapy. Purpose of the study is to assess the effectiveness of combined treatment (surgery + radiomodifier as chemotherapy and radiation therapy) in patients with cervical cancer.

MATERIALS AND METHODS

This study included 661 patients treated at our clinic from 2015 to 2020. At the first stage of treatment, a remote radiation effect is performed on the linear electron accelerator LUEV-15M1 (15 MeV). Uniform irradiation of the small pelvis is performed with 2 constraining fields 15x15 cm or 16x16 cm in the normal fractionation mode Fraction Size (FS) = 2 Gr daily 5 times a week to Total Body Irradiation (TBI) = 20-30 Gr on points A and B. In large exophytic tumors, 1-2 sessions of intra-cavity irradiation are performed using "Microselectron HDR" ("Nucletron", Holland) with forward stepping source of Iridium-192. As a radiosensitizing agent, we used two drugs: cisplatin (CDDP) and capecitabine (Xeloda). Cisplatin is administered once a week (for four weeks) intravenously at a rate of 20 mg/m², up to a total dose of 120 mg. The doses were based upon the studies by P. Rose et al. 1998⁷ and H. Keys et al. 1999,¹⁸ in which cisplatin was administered at the rate of 40 mg/m². Our treatment procedure provides a meaningful increase in the effect of the first stage of treatment with acceptable toxic complications. Capecitabine is administered at a dose of 2000 mg daily, for two weeks together with preoperative radiation exposure. Xeloda is a fluoropyrimidine carbamate derivate and possesses selective cytotoxic effect on the tissue. As a result of selective activation, the content of 5-fluorouracil in the tumor significantly exceeds its levels in healthy tissues, and thus the systemic effect of 5-FU on healthy tissues of the body decreases. At the end of the first stage, we performed a comprehensive assessment of the treatment effectiveness. After 10 to 12 days, patients who could perform radical surgery underwent a radical panhysterectomy with bilateral iliac lymphadenectomy by Wertheim-Meigs.

After the postoperative morphological analysis of the operating material in case of invasion more than 5 mm and up to 1 cm and absence of metastases in regional lymph nodes, remote irradiation of small pelvis from open fields FS = 2 Gr to TRI = 10-14 Gr (42- 44 Gr considering the preoperative course). In case invasion is more than 1 cm and metastatic lesions of regional lymph nodes is present, remote irradiation was performed in the same fractionation mode, totaling to 50-55 Gr. After 4-5 weeks adjuvant single-drug chemotherapy with cisplatin 20 mg/m² for 1-5 days (2 cycles at an interval of 4 weeks) or two cycles of single-drug chemotherapy with the Xeloda 2500 mg/m². In patients who cannot perform radical surgical intervention, combined radiation treatment is preferred. The irradiation of the small pelvis is performed with 2 constraining fields 15x15 cm or 16x16 cm in the normal fractionation mode with TBI = 20, 26, 30 Gr at stages Ib2, IIb, III. Then the central shielding unit is installed and the TBI on the pelvic lymph nodes is increased up to 46 Gr at IIB-III stages. Contact irradiation is performed on "Microselectron HDR" in fractionation mode: FS = 7Gr once a week, TBI = 28 Gr.

After 5-6 weeks since the combined course, the patients were given two cycles of single-drug chemotherapy CDDP 20mg/m² with a break of 4 weeks or two cycles of mono-chemotherapy with capecitabine. We evaluated the clinical effect in the first week after the first treatment stage. By this time, patients in the group with CLL received 4 infusions of cisplatin (Daily Dose = 120 mg) or the total dose of capecitabine is 28000 mg and the total focal radiotherapy dose at point A – 24Gr, while the total focal dose at point A in women from the control group was 30 Gr.

RESULTS

Our approach provided significant increase in the first stage treatment effectiveness while the toxicity remained acceptable. In the main study group, after 10-12 days of combined radiotherapy at linear particle accelerator LUEV-15M1 (15MeV) with a radiomodifier such as cisplatin (CDDP) and capecitabine (Xeloda), 292 (87%) of patients became operable. In result of the first stage treatment, tumor completely regressed in 15 (4.6%) patients, compared to 3 (0.9%) in control group. More than half regression was noted in 162 (48.3%) in the study group, compared to 122 (37.4%) patients. At least quarter reduction is found in 106 (31.4%) patients compared to 68 (21.1%). No response is registered in 53 (15.7%) patients in the study group, compared to 132 (40.6%) in control group. Overall, any response to treatment was achieved in 84.3% in the study group, compared to 59.4% in the control group (p<0.01). It is worth mentioning that in group of patients without tumor reduction, we still observed some definite positive changes, including decrease in size of exophytic part, reduced bleeding and secretions

amounts, reduced in size, or completely dissolved superficial necrotic zone. The presence of parametrial infiltration and its nature are important signs of pathology extent and treatment effectiveness. Results regarding the infiltration are presented in Table 1. Among 336 patients with cervical cancer type IB2 stage III, who received therapy according to scheme chemotherapy – surgery – radiotherapy, 3-year remission rate is 87% (292 patients). The limitation with cytostatic administration is their adverse toxicity. Table 2 shows the percentage and complications severity encountered – in most cases they did not exceed moderate. Regarding the reaction of internal organs to chemoradiation treatment, it can be concluded that the nature and extent of early complications does not reliably differ in both groups (Table 3). Table 4 contains information regarding organs' adverse reaction to chemoradiation.

DISCUSSION

Methods of radiomodification have been developed in the form of non-standard fractionation of the radiation dose, based upon oxygen heterogeneity in tumor tissues. At the same time, several physical and chemical radio-modifiers have been proposed, which have radioprotective and radiosensitizing properties, such as hyperbaric oxygenation, general gas hypoxia by inhalation of the gas mixture with reduced (8-10%) oxygen content during remote gamma-therapy session, use of laser applications and other. To overcome the radio-resistance of several tumors and enhance the effect of ionizing effects of irradiation is performed in combination with electromagnetic, inductive UHF local hyperthermia.

Possibility to enhance radiation of the tumor by creating short-term hyperglycemia with lower tumor pH (6.7 - 5.4) was investigated. According to experimental data, it was found that the anticancer effect of irradiation is inversely proportional to the initial volume of the tumor without clear dependency with the glucose doses.

The most common class of chemical radiomodifiers was previously electron-acceptor compounds, among which high activity as radiosensitizers of hypoxic cells in experiments in vitro and biological models showed compounds of *metronidazole*. Clinical trials showed a certain tendency to improve treatment outcomes for lung cancer, esophagus, head and neck tumors, bladder, and cervix with generally accepted methods of administration metronidazole into the body. The authors, however, point to the frequency of toxic reactions when using metronidazole, starting with a blood level 120 µg/mL, while the best radiosensitizing effect of the drug is achieved when the blood levels are 170-220 µg/mL.^{8,14,19,24} The effectiveness of radiotherapy with intra-tumor administration of metronidazole was expressed in accelerated (in total dose of 36-56 Gy) and complete tumor regression in

54.3% of patients. In control - the radiation treatment without metronidazole, respectively, in 42%. At the same time, the 3-year survival of patients with cervical cancer stage III is $79.7 \pm 4.1\%$.^{1, 9,18} Similar results of 2-3-year survival were obtained in some Ukrainian scientists.^{14, 20, 22,}

Using a combination of cytostatics (vincristine, platydam and adriamycin) in the treatment of common cervical cancer processes, there were noted complications in the form of nausea, vomiting in all patients, alopecia in 96.7%, oppression of hematopoiesis 60% of cases, nephrotoxicity in 40%. In chemotherapy treatment of patients with cervical cancer with inclusion in the treatment regimen 5-fluorouracil and mitomycin C severe hematological complications of the third degree in 5% of patients, dyspepsia in 4% cases.

Comprehensive chemoradiation treatment programs for common cervical cancer with polyradiomodification options were also proposed. Before carrying out and/or in the process of combined radiotherapy with unconventional dose fractionation, administration of 5-fluorouracil is used, supplemented by the introduction of cisplatin or methotrexate in combination with *Ultra High Frequency* (UHF) hyperthermia or sizofara.

It was performed 3 courses of combined chemotherapy (cyclophosphane, bleomycin, cisplatin) in 26 patients with the third stage of cervical cancer followed by radiotherapy. In 44.5% of cases partial tumor *reduction* was noted. Seven patients did not complete the course of chemotherapy due to severe toxicity with one death. Conclusion of the authors: merely chemotherapy for cervical cancer is not effective, toxic and has no survival benefits. The same point of view was in the studies of the 3-year survival rate of cervical cancer patients with the third stage after chemotherapy treatment with generally accepted methods of introducing cytostatic treatment.

Using a combination of cytostatic drugs (cisplatin, bleomycin, vincristine) before the combined radiotherapy, 5-year survival of patients with common processes of cervical cancer was as high as 68%. Using hydroxyurea as a modifying agent during radiotherapy and a 4-week course after its end, it was possible to achieve 60% 5-year survival of patients with cervical carcinoma in stage- III.

It was discovered that performing combined irradiation and parallel systemic administration of cisplatin and 5-fluorouracil achieved a 3-year survival rate in 87% of women with common cervical cancer.

Some authors based on the results of randomized studies have registered a significant increase in relapse-free survival of patients receiving radiochemotherapy with cisplatin, hydroxyurea, and 5-Fluorouracil at acceptable toxic phenomena, which eventually served as a recommendation for the use of chemotherapy as a standard for treating patients with cervical cancer. The study of preoperative radiochemothera-

py demonstrated its effectiveness in improving operability. Reports on the use of intra-arterial chemotherapy in common processes of cervical cancer in terms of supplementing combined radiotherapy are heterogeneous. Clinical material of studies is small in volume (groups of patients with cervical cancer stage III for 10-14 patients), and there was different composition of used cytostatics.^{9, 21, 23}

It might be necessary to extend current investigation in the future to controlled randomized environment to confirm our approach on larger group of the patients.

CONCLUSION

The undeniable advantage of radiation as an independent method and as combined with chemotherapy has been proven. It can be concluded that the main method of exposure is radiotherapy, as an independent method and as a component in combined treatment.

The weekly administration of platinum as well as fluoropyrimidine radio-modifying agents can be considered as current standard. All the above only confirms the need for further research in this direction and perhaps developing not only new cytostatic therapy protocols in combination with radiotherapy, but also the synthesis of fundamentally new drugs.

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int. J. Cancer* 2015;136(5): 359-386.
2. American Cancer Society: Cancer Facts and Figures 2020. Atlanta, Ga: American Cancer Society, 2020,4, tab1.
3. Fedorenko Zoja P., Michailovich Youriy Yo., Goulak Lyudmyla O., Gorokh Yevgeniy L., Ryzhov Anton Yu., Soumkina Olena V., et al. Bulletin of national cancer registry of Ukraine 2020; 21:6.
4. Fedorenko ZP., Michailovich Y Yo., Goulak LO., Gorokh YL., Ryzhov AY., Soumkina OV., et al. Bulletin of national cancer registry of Ukraine 2020;21:10.
5. Myong ChL, Maria L, Seung HS. Practice guidelines for management of cervical cancer in Korea: a Korean Society of Gynecologic Oncology Consensus Statement. *J Gynecol Oncol.* 2017; 28(3):22.
6. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. *Int J Gynaecol Obstet* 2018; 143(2):22.
7. Rose PG, Blessing JA, Mayer AR, Homesley HD. Prolonged oral etoposide as second-line therapy for platinum-resistant and platinum-sensitive ovarian carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol.* 1998;16(2):405-410.
8. Chino J, Annunziata CM, Beriwal S. Radiation Therapy for Cervical Cancer: Executive Summary of an ASTRO Clinical Practice Guideline. *Pract Radiat Oncol* 2020; 10:220.
9. Vishnevskaya EE. Handbook of Oncology Gynecology. Minsk, Belarus. 2014.
10. Dexter LI., Maryanenko AI., Bohman YaV. Changes in clinical and immunological parameters in patients with cervical cancer under the influence of a polypeptide drug thymus (thymalin). *Immunology of tumors.* Riga: Zinatne, 2012. 150-152.
11. Bernardini M, Barrett J, Seaward G, Covens A. Pregnancy outcomes in patients after radical trachelectomy. *Am J Obstet Gynecol.* 2003; 189: 1378-1382.
12. Boss EA, van Golde RJ, Beerendonk CC, Massuger LF. Pregnancy after radical trachelectomy: a real option. *Gynecol Oncol.* 2005; 99: 152-156
13. American College of Obstetricians and Gynecologists ACOG practice bulletin. Diagnosis and treatment of cervical carcinomas. American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet.* 2002; 78: 79-91.
14. Weinberg M, Radiation therapy. Retrospection, looking to the future. *J Med Radio* 1994\$ 39 (3): 68-71.
15. Keys HM, Bundy BN, Stehman FB, Mudderspach LI, Chafe WE, Suggs CL 3rd, Walker JL, Gersell D. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med.* 1999; 340(15):1154-1161.
16. Stolyarova KV, Vinokurov VL., Zharinov GM. Results of polyradiomodification in radiation therapy for cancer of the cervix and uterine body. *Med Radiol.* 2012; 3-4: 273-281.
17. Bohman YaV., Vishnevsky AS., Maksimov SYa. Petersburg scale of oncogynecology: some results and prospects. *Vopr. onkol.* 1997; 43(1):39-46.
18. Narimatsu A., Ito T. Neoadjuvant chemotherapy with continuous intraarterial infusion fCDDP, 5Fu in the treatment of advance cervical and endometrial adenocarcinoma. *J. Jap. Soc. Cancer Then* 2005; 30(2): 408.
19. Vishnevskaya EE., Kosenko IA. Long-term results of complex therapy of patients with cervical cancer with a palate prognosis. *Vopr. onkol.* 2009; 45(4): 420-423.
20. Alvarez SA., Harvilevsky LJ., Bae JV. *Gyneacol. Oncol.* 2007; 107(2).
21. Krikunova LI., Mkrtchan LS., Shentereva NI., Sychenkova NI. Cervical cancer. *Therapeutic Radiology: A Guide for Physicians.* LLC "MK", Moscow 2010; 369-378.
22. Stolyarova KV, Vinokurov VL., Zharinov GM. Results of polyradiomodification in radiation therapy for cancer of the cervix and uterine body. *Med Radiol.* 2012; 3-4: 281-292.
23. Greenlee R., Murray T., Bolden S. Cancer statistics. *CA Cancer J. Clin.* 2001; 36: 5115.
24. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Cervical cancer.

Table 1: Dynamics of tumor size after the first stage of treatment

A result of the first stage of treatment	Groups	
	Study Group abs (%)	Monitoring Group abs (%)
Full regress of the clinically visualized tumor	15 (4.6)	3 (0.9)
Reduction of more than 50% of the original size tumor	162 (48.3)	122 (37.4)
Regress of the neoplasm by more than 25%, but not exceeding 50%	106 (31.4)	68 (21.1)
Did not respond to therapy	53 (15.7)	132 (40.6)

Table 2: Dynamics of infiltration of parameter fiber because of therapy

Reaction of parametric infiltrates	Groups		
	Study Group n=336 people abs (%) CDDP n=313	Xeloda n=23	Monitoring Group n=325 people abs (%)
Disappearance	124 (39.4)	6 (32.5)	93 (28.5)
Reduction by 1/2 of the original	149 (47.7)	10 (44.2)	132 (40.7)
No changes	40 (12.9)	5 (23.3)	100 (30.8)

Table 3: Hematological complications in chemoradiation therapy

Complications	Groups	
	Study Group abs (%)	Monitoring Group abs (%)
Leukopenia	19 (5.6)	10 (3.2)
Thrombocytopenia	9 (2.8)	6 (1.8)
Anemia	12 (3.7)	13 (4.0)

Table 4: Characteristics of reactions of internal organs to chemoradiation treatment

Complications	Study Group abs (%)	Control group abs (%)
Post-beam rectitis	16 (4.6)	16 (5.1)
Post-beam cystitis	19 (5.6)	11 (3.4)
Nausea, vomiting	28 (8.4)	13 (4.1)